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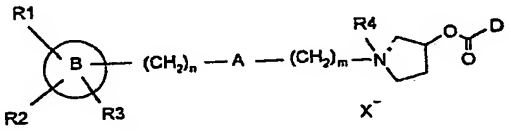
DIAGRAM (ONLY FOR INTERPRETATION OF THE ABSTRACT)



54 TITLE

New pyrrolidinium derivatives

57 ABSTRACT

New pyrrolidinium derivatives having the chemical structure of general formula (I)

and processes for their preparation, pharmaceutical compositions comprising them and their use in therapy as antagonists of the M_3 muscarinic receptors.

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Intérprete Jurado del idioma inglés

NOVEL PYRROLIDINIUM DERIVATIVES

This invention relates to novel therapeutically-useful pyrrolidinium derivatives, to some methods for their preparation and to pharmaceutical compositions containing them.

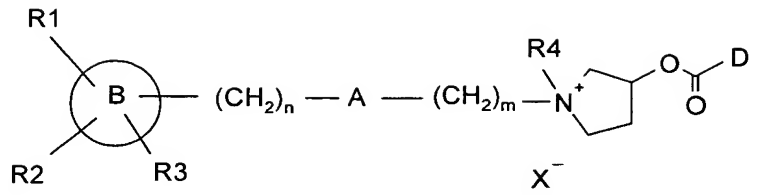
The novel structures according to the invention are antimuscarinic agents with a potent and lasting effect. In particular, these compounds display high affinity for the M_3 muscarinic receptors. This muscarinic receptor subtype is present in glands and smooth muscles and acts as a mediator of the excitatory effects of the parasympathetic system on glandular secretion and on contraction of visceral smooth muscle (Chapter 6, Cholinergic Transmission, in H.P. Rang et al., Pharmacology, Churchill Livingstone, New York, 1995).

It is known that M_3 antagonists can be used for treating diseases characterized by an increase in parasympathetic tone, by excessive glandular secretion and by smooth muscle contraction (R.M. Eglen and S.S. Hegde, (1997), Drug News Perspect., 10(8):462-469).

Examples of this category of diseases are respiratory disorders such as chronic obstructive pulmonary disease (COPD), bronchitis, bronchial hyperreactivity, asthma, cough and rhinitis; urological disorders, such as urinary incontinence, pollakiuria, neurogenic or unstable bladder, cystospasm and chronic cystitis; gastrointestinal disturbances, such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulcers; and cardiovascular disorders, such as vagus-induced sinus bradycardia (Chapter 7, Muscarinic Receptor Agonists and Antagonists, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th edition, McGraw Hill, New York, 2001).

The compounds of the invention can be used alone or combined with other drugs that are effective in the treatment of these diseases. For example, they can be administered in combination with β_2 agonists, steroids, anti-allergic drugs, phosphodiesterase IV inhibitors and/or leukotriene D4 (LTD4) antagonists for simultaneous, separate or sequential use in the treatment of a respiratory disease.

The novel pyrrolidinium derivatives of the invention have the chemical structure of formula (I):



(I)

in which

B is a phenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl or biphenyl group or a 5- to 10-membered heteroaromatic group containing one or more, for example 1, 2, 3 or 4, heteroatoms selected from N, O or S;

R^1, R^2 and R^3 each represent, independently, a hydrogen or a halogen atom, or a hydroxy, phenyl, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-NHCOR^5$, $-CONR^5R^6$, -CN, $-NO_2$, $-COOR^5$ or $-CF_3$ group or a linear or branched lower alkyl group, optionally substituted;

or R^1 and R^2 together form an aromatic or alicyclic ring or a heterocyclic group;

R^5 and R^6 each represent, independently, a hydrogen atom, a linear or branched lower alkyl group, optionally substituted, or together form an alicyclic ring;

n is an integer from 0 to 4;

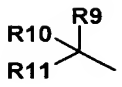
A represents a group selected from $-CH_2-$, $-CH=CR^7-$, $-CR^7=CH-$, $-CR^7R^8-$, -CO-, -O-, -S-, -S(O)-, $-S(O)_2-$ and $-NR^7-$, in which R^7 and R^8 each represent, independently, a hydrogen atom, a linear or branched lower alkyl group, optionally substituted, or together form an alicyclic ring;

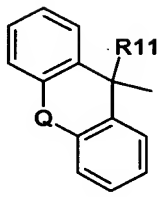
m is an integer from 0 to 8;

R^4 represents a lower alkyl group;

D represents a group of formula i) or ii)

i) ii)





in which

R^9 represents a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl or 3-thienyl;

R^{10} represents a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl or C_3-C_7 cycloalkyl;

and R^{11} represents a hydrogen atom or a hydroxy, methyl or $-CH_2OH$ group;

the cyclic groups represented by R^9 and R^{10} being optionally substituted with one or two substituents selected from halogen, linear or branched lower alkyl optionally substituted, hydroxy, alkoxy optionally substituted, nitro, cyano, $-CO_2R^{12}$ or $-NR^{12}R^{13}$, in which R^{12} and R^{13} are identical or different and are selected from hydrogen and linear or branched lower alkyl groups, optionally substituted;

Q represents a single bond or a group $-CH_2-$, $-CH_2-CH_2-$, $-O-$, $-O-CH_2-$, $-S-$, $-S-CH_2-$ or $-CH=CH-$;

X^- represents a pharmaceutically acceptable anion of a monovalent or polyvalent acid;

including all the individual stereoisomers and mixtures thereof;

with the condition that in the compounds in which B is phenyl, R^9 is unsubstituted phenyl, R^{10} is unsubstituted phenyl or unsubstituted C_3-C_7 cycloalkyl, R^{11} is hydrogen or hydroxy, and then the sequence $-(CH_2)_n-A-(CH_2)_m-$ cannot be one of methylene, ethylene or propylene.

Other aims of the present invention are to provide methods for preparing said compounds, pharmaceutical compositions that contain an effective amount of said compounds; the use of the compounds in the manufacture of medicinal products for the treatment of diseases that can be treated by antagonism of the M_3 muscarinic receptors;

and methods of treatment of diseases that can be treated by antagonism of M_3 muscarinic receptors, said methods comprising the administration of the compounds of the invention to a subject who needs said treatment.

Certain esters of 3-pyrrolidinol, including some pyrrolidinium derivatives, which are outside of the scope of the present invention, were described in US patent 2,956,062.

In the quaternary ammonium compounds of the present invention, represented by formula (I), an equivalent of an anion (X^-) combines with the positive charge of the N atom. X^- can be an anion of various mineral acids, for example chloride, bromide, iodide, sulphate, nitrate, phosphate, or an anion of an organic acid, for example acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, trifluoroacetate, methanesulphonate and p-toluenesulphonate. X^- is preferably an anion selected from chloride, bromide, iodide, sulphate, nitrate, acetate, maleate, oxalate, succinate or trifluoroacetate. More preferably X^- is chloride, bromide, trifluoroacetate or methanesulphonate.

As used in the present specification, an alkyl group can be linear or branched, and is typically a lower alkyl group. A lower alkyl group contains from 1 to 8, preferably from 1 to 6 and more preferably from 1 to 4, carbon atoms. In particular it is preferred for said alkyl group to be represented by a methyl, ethyl, propyl, including i-propyl, or butyl including n-butyl, sec-butyl and tert-butyl group.

The optionally substituted lower alkyl groups mentioned here include linear or branched alkyl groups containing from 1 to 8, preferably from 1 to 6, more preferably from 1 to 4, carbon atoms as mentioned previously, which can be substituted or unsubstituted in any position with one or more substituents, for example with 1, 2 or 3 substituents. When two or more substituents are present, each one can be the same or different. The substituent or substituents are typically halogen atoms, preferably fluorine atoms or hydroxy or alkoxy groups.

The alkoxy groups mentioned here are typically lower alkoxy groups, i.e. groups that contain from 1 to 8, preferably from 1 to 6 and more preferably from 1 to 4, carbon atoms, the hydrocarbon chain being linear or branched and being optionally substituted in any position with one or more substituents, for example with 1, 2 or 3 substituents. When two or more substituents are present, each one can be the same or different. The substituents are typically halogen atoms, preferably fluorine atoms. The preferred

alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec-butoxy, t-butoxy, difluoromethoxy and trifluoromethoxy.

The cycloalkyl groups and the alicyclic groups mentioned here, unless otherwise specified, typically contain from 3 to 8 carbon atoms, preferably from 3 to 6 carbon atoms. The cycloalkyl groups and alicyclic rings of 3 to 6 carbon atoms include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The cycloalkyl groups that contain from 3 to 7 carbon atoms include cycloalkyl groups of 3 to 6 carbon atoms and cycloheptyl.

As used in the present specification an aromatic ring or group typically contains from 5 to 14, preferably from 5 to 10, carbon atoms. Examples of aromatic groups include phenyl and naphthalenyl.

A heterocyclic or heteroaromatic group mentioned here is generally a 5- to 10-membered group, such as a 5-, 6- or 7-membered group that contains one or more heteroatoms selected from N, S and O. Typically, 1, 2, 3 or 4 heteroatoms are present, preferably 1 or 2 heteroatoms. A heterocyclic or heteroaromatic group can be a single ring or two or more condensed rings in which at least one ring contains a heteroatom. Examples of heterocyclic groups include piperidyl, pyrrolidyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, imidazolyl, imidazolidinyl, pyrazolinyl, indolinyl, isoindolinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, quinuclidinyl, triazolyl, pyrazolyl, tetrazolyl and thienyl. Examples of heteroaromatic groups include pyridyl, thienyl, furyl, pyrrolyl, imidazolyl, benzothiazolyl, pyridinyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, triazolyl and pyrazolyl.

As used in the present specification, a halogen atom includes an atom of fluorine, chlorine, bromine or iodine, generally a fluorine, chlorine or bromine atom.

The preferred compounds of formula (I) are those in which B represents a phenyl, pyrrolyl, thienyl, furyl, biphenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, imidazolyl or benzothiazolyl group. More preferably B represents a phenyl, thienyl or pyrrolyl group.

B can be unsubstituted or can be substituted with 1, 2 or 3 groups (R^1 to R^3) which can be in any position in the ring.

In the preferred compounds of the invention R^1, R^2 and R^3 each represent, independently, a hydrogen or halogen atom, or a hydroxy, methyl, tert-butyl, $-CH_2OH$, 3-hydroxypropyl -OMe, $-NMe_2$, -NHCOMe, $-CONH_2$, -CN, $-NO_2$, -COOMe or $-CF_3$ group. In the more preferred compounds R^1, R^2 and R^3 are hydrogen, fluorine, chlorine or hydroxy.

Generally B is unsubstituted or is substituted with a group, for example when B is a phenyl group it can be substituted in the 2, 3 or 4 position. Examples of substituted phenyl groups that can represent B are tolyl including o-, m- and p-tolyl, 3-cyanophenyl, 2-, 3- and 4-hydroxyphenyl and 2-, 3- and 4-fluorophenyl.

The preferred compounds of formula (I) are those in which n = 0 or 1; m is an integer from 1 to 6, especially 1, 2 or 3; and A represents a $-CH_2-$, -CH=CH-, -CO-, -NMe-, -O- or -S- group. The more preferred compounds are those in which A is a $-CH_2-$, -CH=CH- or -O- group.

Other preferred compounds of formula (I) are those in which the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylalyl, phenethyl, 4-phenylbutyl, 3-phenylpropyl, 3-(2-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 2-benzyloxyethyl, 3-pyrrol-1-ylpropyl, 2-thien-2-ylethyl, 3-thien-2-ylpropyl, 3-phenylaminopropyl, 3-(methylphenylamino)propyl, 3-phenylsulphanylpropyl, 3-o-tolyloxypropyl, 3-(2,4,6-trimethylphenoxy)propyl, 3-(2-tert-butyl-6-methylphenoxy)propyl, 3-(biphenyl-4-yloxy)propyl, 3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)-propyl, 3-(naphthalen-2-yloxy)propyl, 3-(naphthalen-1-yloxy)propyl, 3-(2-chlorophenoxy)propyl, 3-(2,4-difluorophenoxy)propyl, 3-(3-trifluoromethylphenoxy)propyl, 3-(3-cyanophenoxy)propyl, 3-(4-cyanophenoxy)propyl, 3-(3-methoxyphenoxy)propyl, 3-(4-methoxyphenoxy)propyl, 3-(benzo[1,3]dioxol-5-yloxy)propyl, 3-(2-carbamoylphenoxy)propyl, 3-(3-dimethylaminophenoxy)propyl, 3-(4-nitrophenoxy)propyl, 3-(3-nitrophenoxy)propyl, 3-(4-acetylaminophenoxy)propyl, 3-(4-methoxycarbonylphenoxy)propyl, 3-[4-(3-hydroxypropyl)phenoxy]propyl, 3-(2-hydroxymethylphenoxy)propyl, 3-(3-hydroxymethylphenoxy)propyl,

3-(4-hydroxymethylphenoxy)propyl, 3-(2-hydroxyphenoxy)propyl, 3-(4-hydroxyphenoxy)propyl, 3-(3-hydroxyphenoxy)propyl, 4-oxo-4-thien-2-ylbutyl, 3-(1-methyl-[1H]-imidazol-2-ylsulphanyl)propyl, 3-(benzothiazol-2-yloxy)propyl, 3-benzyloxypropyl, 6-(4-phenylbutoxy)hexyl, 4-phenoxybutyl, 4-(4-fluorophenyl)-4-oxobutyl or 4-oxo-4-phenylbutyl.

Compounds that are more preferred are those in which the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylalyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 3-thien-2-ylpropyl, 4-oxo-4-thien-2-ylbutyl, 2-benzyloxyethyl, 3-o-tolyloxypropyl, 3-(3-cyanophenoxy)propyl, 3-(methylphenylamino)propyl, 3-phenylsulphanylpropyl, 4-oxo-4-phenylbutyl, 4-(4-fluorophenyl)-4-oxobutyl, 3-(2-chlorophenoxy)propyl, 3-(2,4-difluorophenoxy)propyl, 3-(4-methoxyphenoxy)propyl and 3-(benzo[1,3]dioxol-5-yloxy)propyl.

Examples of especially preferred compounds are those in which the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylalyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 4-(4-fluorophenyl)-4-oxobutyl or 3-thien-2-ylpropyl.

Other preferred compounds of formula (I) are those in which D is a group of formula i), and in which R^9 is a group selected from phenyl, 2-thienyl or 2-furyl; R^{10} is a group selected from phenyl, 2-thienyl, cyclohexyl or cyclopentyl; and R^{11} is a hydroxy group.

Preferred compounds of formula (I) are also those in which D is a group of formula ii) and in which Q is a single bond or an oxygen atom and R^{11} is a hydrogen atom or a hydroxy group.

The compounds of the present invention represented by formula (I) described above have an asymmetric quaternary nitrogen in the pyrrolidinium ring and also have one or more asymmetric carbons, for example the carbon in position 3 of the pyrrolidinium ring; the carbon substituted with R^9, R^{10} and R^{11} in the compounds of formula (I) in which D is a group of formula i); or the carbon that is bound to the carbonyl group in the compounds of formula (I) in which D is a group of formula ii). Each one of these four asymmetric atoms can have R or S configuration. The isomers alone and the mixtures of isomers fall within the scope of the invention.

Particular individual compounds of the invention include:

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium trifluoroacetate

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-thien-2-ylpropyl)pyrrolidinium bromide

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl) pyrrolidinium bromide

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylalil)pyrrolidinium trifluoroacetate

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(4-oxo-4-thien-2-ylbutil)pyrrolidinium trifluoroacetate

1-[4-(4-Fluorophenyl)-4-oxobutil]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium trifluoroacetate

1-Ethyl-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-hydroxyphenoxy)propyl]pyrrolidinium trifluoroacetate

3-(2-Hydroxy-2,2-dithien-2-yl-acetoxy)-1-methyl-1-(3-pyrrol-1-ylpropyl)pyrrolidinium trifluoroacetate

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-[6-(4-phenylbutoxy)hexyl]pyrrolidinium trifluoroacetate

1-(2-Benzyloxyethyl)-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium trifluoroacetate

1-[3-(3-Cyanophenoxy)propyl]-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium trifluoroacetate

3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methyl-1-[3-(naphthalen-1-yloxy)propyl]pyrrolidinium trifluoroacetate

3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methyl-1-[3-(methylphenylamino)propyl]pyrrolidinium trifluoroacetate

3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-ethyl-1-(3-phenylsulphanylpropyl)pyrrolidinium trifluoroacetate

1-[3-(Benzothiazol-2-yloxy)propyl]-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium trifluoroacetate

3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(2,4,6-trimethylphenoxy)propyl]pyrrolidinium trifluoroacetate
1-[3-(2-Chlorophenoxy)propyl]-3-(2-cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methylpyrrolidinium trifluoroacetate
3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(3-trifluoromethylphenoxy)propyl]pyrrolidinium trifluoroacetate
1-[3-(Biphenyl-4-yloxy)propyl]-3-(2-cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methylpyrrolidinium trifluoroacetate
3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-[3-(2,4-difluorophenoxy)propyl]-1-methylpyrrolidinium trifluoroacetate
3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-ethyl-1-[3-(4-methoxyphenoxy)propyl]-pyrrolidinium trifluoroacetate
3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyl]pyrrolidinium trifluoroacetate
3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(1-methyl-1H-imidazol-2-ylsulphanyl)propyl]pyrrolidinium trifluoroacetate
1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide
1-Methyl-1-(3-phenoxypropyl)-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide
1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate
1-[3-(2-Carbamoylphenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate
1-[3-(3-Dimethylaminophenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate
1-[3-(4-Acetylaminophenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate
1-[3-(4-Methoxycarbonylphenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate
1-Methyl-1-[3-(4-nitrophenoxy)propyl]-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate, and
1-[3-(4-Hydroxymethylphenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate.

Particular isomers of the compounds of the invention include:

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide

(1*, 3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide (diastereoisomer 1)
(1*, 3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide (diastereoisomer 2)
(3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide
(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide
(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereoisomer 1)
(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereoisomer 2)
(3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide
(1*,3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereoisomer 1)
(1*,3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereoisomer 2)
(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-thien-2-ylpropyl)pyrrolidinium bromide
(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide
(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 1)
(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 2)
(3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide
(3R)-3-[(2R)-2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy]-1-ethyl-1-(3-phenylsulphanylpropyl)pyrrolidinium trifluoroacetate
(3S)-3-[(2R)-2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy]-1-ethyl-1-(3-phenylsulphanylpropyl)pyrrolidinium trifluoroacetate
(3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide
(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 1)
(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-

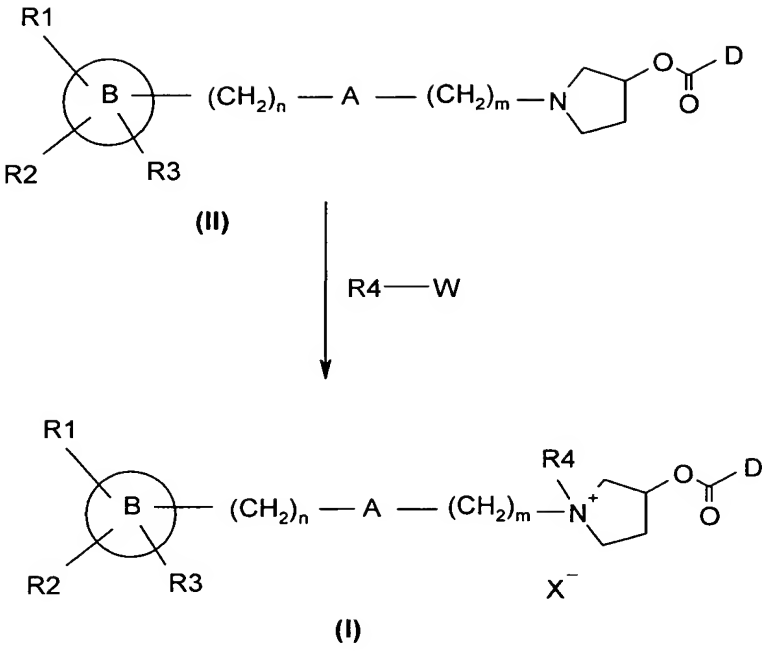
phenoxypropyl)pyrrolidinium bromide (diastereoisomer 2)
(3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide
(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 1)
(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 2)
(3R)-3-[(2S)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide
(3S)-3-[(2S)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide
(3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide
(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereoisomer 1)
(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereoisomer 2), and
(3S)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide.

((*): indeterminate configuration; both the (1R) isomer and the (1S) isomer of the above compounds can be formed. Designated (1R) and (1S) for convenience.

According to another embodiment, the present invention provides methods for preparing the novel pyrrolidinium derivatives of formula (I). These compounds can be produced by two different methods, described below as method (a) and method (b).

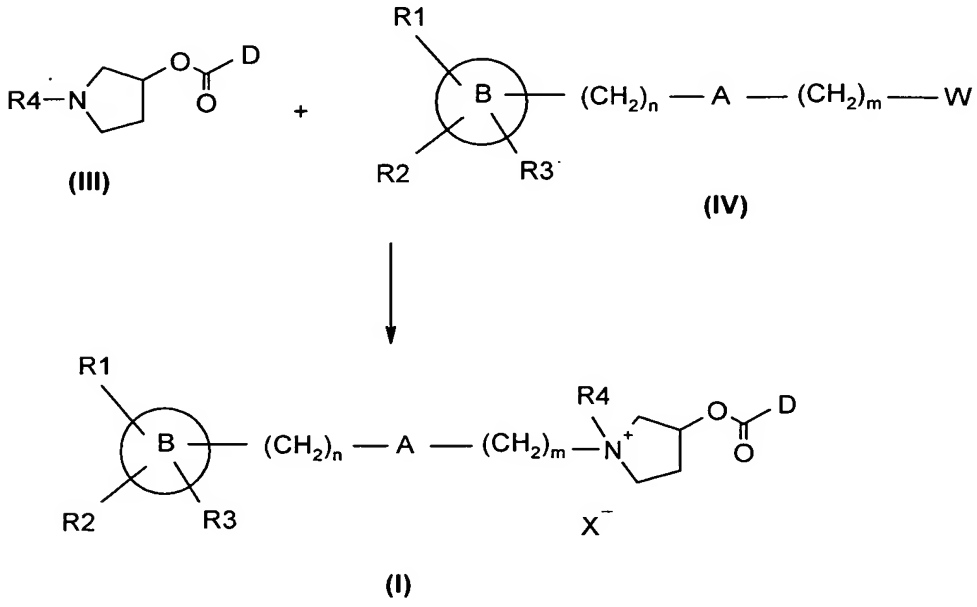
In accordance with method (a), the compounds of formula (I) are obtained by reaction of an alkylating agent of formula R4-W with the intermediates of formula (II).

Method a



In accordance with method (b), the compounds of formula (I) are prepared by reaction of an alkylating agent of formula (IV) with the intermediates of formula (III).

Method b



In formulae (I), (II), (III) and (IV), m, n, A, B, D, R1, R2, R3 and R4 and X^- are as

defined previously.

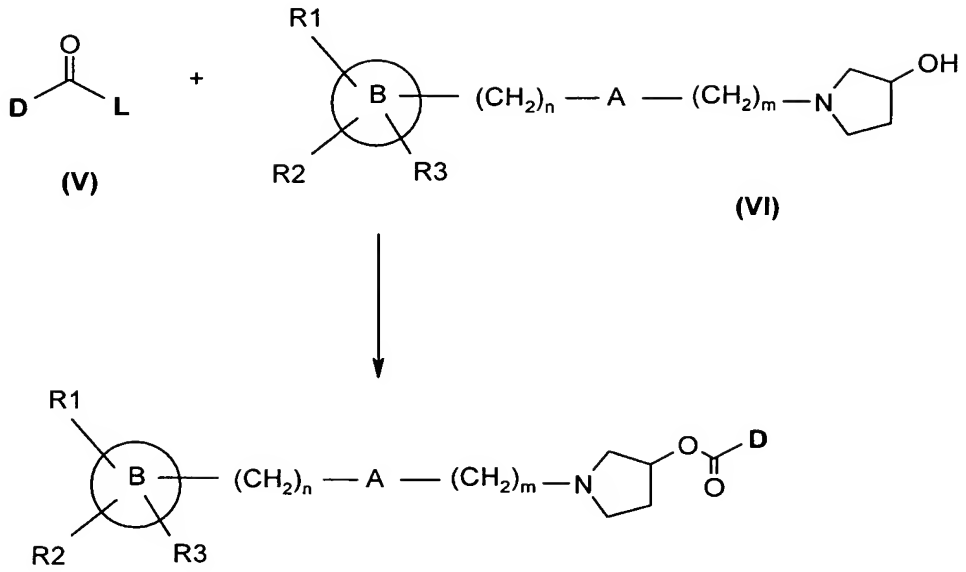
In formulae (IV) and R4-W, W represents any suitable removable group, such as a group X as defined previously for the compounds of formula (I). Preferably, W represents a group X. When W represents a group different from X, the quaternary ammonium salt of formula (I) is produced starting from the product of method (a) or (b) by an exchange reaction according to the standard methods for replacing the anion W^- with the desired anion X^-.

Methods (a) and (b) can be carried out by known experimental methods of conventional synthesis, or using methods of solid phase extraction, which permit various compounds to be prepared in parallel.

The diastereoisomers of the compounds of formula (I) can be separated by conventional methods, for example by chromatography or crystallization.

The intermediates of formula (II) used in method (a) can be produced by reaction of a compound of formula (V) with a compound of formula (VI) as shown in the following method (c).

Method c



In formulae (II), (V) and (VI), m, n, A, B, D, R1, R2 and R3 are as defined previously.

The pyrrolidinol esters of formula (II) can be converted to pharmaceutically acceptable salts by methods that are known in the prior art. Typically, an ester of formula (II) is treated with an inorganic or organic acid such as oxalic, fumaric, maleic, tartaric, succinic or hydrochloric acid.

The pyrrolidinol esters of formula (II) that have one or more asymmetric carbons, include all possible stereoisomers, the isomers alone and mixtures of isomers.

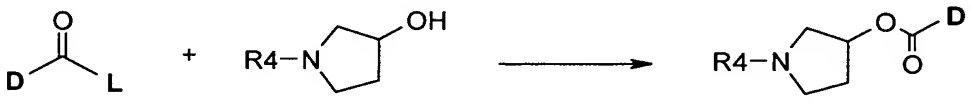
The diastereoisomers of the compounds of formula (II) can be separated by conventional methods, for example by chromatography or crystallization. Certain compounds of formula (II) are novel and fall within the scope of the present invention. In particular:

(3R)-1-(2-phenoxyethyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid
(3R)-1-(3-phenoxypropyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid
(3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid, and

(3R)-1- phenethylpyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid.

The compounds of formula (III), used in method (b), can be prepared by reaction of a compound of formula (V) with a compound of formula (VII) as described in method (d), shown below.

Method d



(V) (VII) (III)

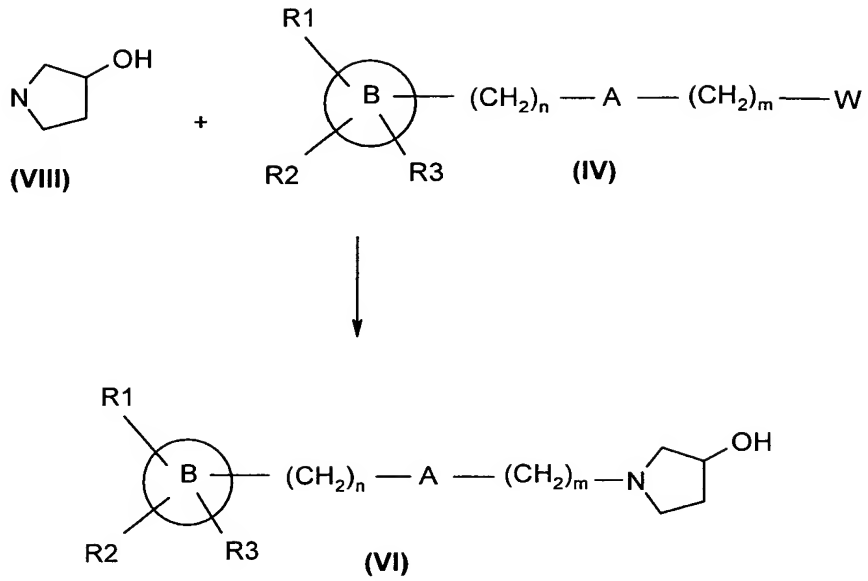
In the compounds of formulae (V), (III) and (VII), D and R4 are as described previously for the compounds of formula (I); and L in formula (V) represents a removable group. For example, L can be a chlorine atom, an imidazol-1-yl group or a lower alkoxy group, such as a methoxy group.

The intermediates of formula (V) can be prepared by methods described in the bibliography given later, in the experimental section.

The pyrrolidinol esters of formula (III) that have one or more asymmetric carbons include all the possible stereoisomers, isomers alone and mixtures of stereoisomers. The diastereoisomers of the compounds of formula (III) can be separated by conventional methods, for example by chromatography or crystallization.

The compounds of formula (VI), described in method (c), can be prepared by reaction of an alkylating agent of formula (IV), in which W is a halogen or a sulphonate ester, with the corresponding pyrrolidinol of formula (VIII), as shown in method (e) hereunder.

Method e



In formulae (IV) and (VI), m, n, A, B, R1, R2, R3 and W are as defined previously.

Certain compounds of formula (VI) are novel and fall within the scope of the present invention. In particular:

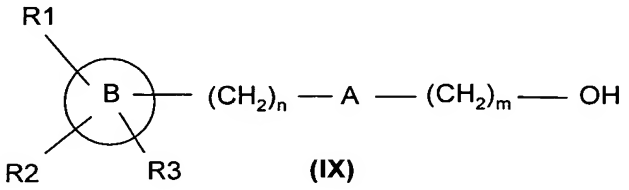
(3R)-1-(3-phenoxypropyl)pyrrolidin-3-ol and
(3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-ol.

The compounds of formula (VII), described in method (d), which are not available commercially, can be produced by synthesis according to general methods, for example by reaction of a compound of formula (VIII) with the corresponding alkylating agent, or by reaction of a compound of formula (VIII) with the corresponding aldehyde and a reducing agent. A particular example is described as method (f) in the experimental section.

Examples of compounds of formula (VIII) that are available commercially are pyrrolidin-3-ol, (3R)-pyrrolidin-3-ol, (3S)-pyrrolidin-3-ol.

The compounds of formula (IV) which are not available commercially have been prepared by synthesis according to general methods. For example, the compounds in which n is 0 and A is one of -O-, -S- or -NR^7, where R^7 is as defined previously, were

obtained by reaction of the corresponding alcohol derivative or its potassium salt with an alkylating agent of formula Y-$(CH_2)_m$-W, in which W is as defined previously and Y can be a halogen atom or a sulphonate ester. Other examples are compounds of formula (IV), in which n is at least 1, which were synthesized starting from the corresponding alcohol derivative of formula (IX) by methods that are well known in industry.



(IX)

The following examples of preparation are intended to illustrate, but not limit the experimental methods described above.

Method (a). Preparation of compounds of formula (I)
Method (b). Preparation of compounds of formula (I)
Method (c). Preparation of compounds of formula (II)
Method (d). Preparation of compounds of formula (III)
Method (e). Preparation of compounds of formula (VI) and
Method (f). Preparation of compounds of formula (VII).

The structures of the compounds obtained were confirmed by ^{1}H-NMR and MS. The NMR spectra were recorded using a Varian 300 MHz instrument. The chemical shifts are expressed as parts per million (δ) of the tetramethylsilane internal reference. The purity of the compounds was determined by HPLC, using reverse-phase chromatography in a Waters instrument. The optical rotations were measured using a PERKIN-ELMER 241 MC polarimeter and molecular ions were produced by mass spectrometry with electrospray ionization in a Hewlett Packard instrument.

Method (a)

Example 6

Preparation of (3R)-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-thien-2-ylpropyl)pyrrolidinium bromide

0.3 g (0.00069 mol) of (3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid (intermediate I-3) was dissolved in 4 ml of acetonitrile and

6 ml of $CHCl_3$. 3.45 ml (0.00345 mol) of a 1M solution of methyl bromide in acetonitrile was added to this solution. After stirring the mixture at room temperature under an N_2 atmosphere for 24 h, the solvents were evaporated. Ether was added to the residue and the mixture was stirred until a solid was obtained. This solid was treated with ether several times, filtered and washed with ether. The yield was 0.34 g (93.2%) of the title compound as a mixture of two stereoisomers.

^{1}H-NMR: mixture of diastereoisomers 55:45.

^{1}H-NMR (DMSO-d_6): δ 1.95-2.20 (m, 3H), 2.60-2.80 (m, 2H), 2.80-2.90 (m, 1H), 2.94 and 3.10 (s, 3H), 3.20- 3.45 (m, 2H), 3.45-3.95 (m, 4H), 5.52 (m, 1H), 6.90-7.05 (m, 4H), 7.10-7.20 (m, 2H), 7.37 (m, 1H), 7.40-7.55 (m, 3H).

MS $[M-Br]^+$: 448

Example 9

Preparation of (1*,3R)-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 1)

Example 10

Preparation of (1*,3R)-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 2)

Following the procedure described in Example 6, 1.6 g of a mixture of two stereoisomers of (3R)-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (compound described in Example 8) was prepared starting from (3R)-1-(3-phenoxypropyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid, intermediate I-2, and a 1M solution of methyl bromide in acetonitrile. The resulting compound was purified by chromatography on silica gel performing gradient elution using chloroform plus isopropanol as eluent (50 → 100%). The appropriate fractions were combined and were evaporated, giving the two title compounds. The structure was confirmed by ^{1}H-NMR.

Diastereoisomer 1 (first diastereoisomer eluted), 0.628 g was obtained (80.1% based on a single isomer).

m.p.: 86.2-89.6°C.

^{1}H-NMR:: diastereoisomer 1 (diastereoisomer 2 not observed)

^{1}H-NMR (DMSO-d_6): δ 2.10-2.30 (m, 3H), 2.65-2.80 (m, 1H), 3.0 (s, 3H), 3.50-3.65 (m, 3H), 3.70-3.85 (m, 2H), 3.85-3.95 (m, 1H), 4.05 (m, 2H), 5.54 (m, 1H), 6.90-7.05 (m, 5H), 7.10-7.20 (m, 2H), 7.25-7.35 (m, 2H), 7.50-7.55 (m, 3H).

MS $[M-Br]^+$: 458

(* Configuration not assigned)

Diastereoisomer 2 (second diastereoisomer eluted) 0.559 g (71.3% based on a single

isomer).
m.p.: 87.1-89.0°C
^{1}H-NMR: diastereoisomer 2 (diastereoisomer 1 not observed).
^{1}H-NMR (DMSO-d_6): δ 2.05-2.30 (m, 3H), 2.65-2.80 (m, 1H), 3.15 (s, 3H), 3.40-3.55 (m, 2H), 3.55-3.80 (m, 3H), 3.95 (m, 3H), 5.55 (m, 1H), 6.90-7.05 (m, 5H), 7.05-7.20 (m, 2H), 7.30-7.40 (m, 2H), 7.45-7.50 (m, 3H).
MS $[M-Br]^+$: 458
(* Configuration not assigned).

Method (b)

Example 7
Preparation of 3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide

0.66 g (0.002 mol) of 1-methylpyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid (intermediate I-7) was dissolved in 9 ml of $CHCl_3$ and 6 ml of acetonitrile. 1.6 ml of 3-(bromopropoxy)benzene (2.15 g, 0.01 mol) was added and the mixture was stirred for 72 hours at room temperature under N_2 atmosphere. The solvents were evaporated. Ether was added to the residue and the mixture was stirred until a solid was obtained. The solid was treated several times with ether, filtered and washed with ether. The yield was 0.75 g (69.4%) of the title compound as a mixture of 4 stereoisomers.
m.p.: 55.3-56.8°C.
^{1}H-NMR: mixture of diastereoisomers 56:44.
^{1}H-NMR (DMSO-d_6): δ 2.05-2.30 (m, 3H), 2.60-2.80 (m, 1H), 2.96 and 3.12 (s, 3H), 3.40-3.50 (m, 1H), 3.50-3.82 (m, 4H), 3.85-4.0 (m, 2H), 4.0-4.10 (m, 1H), 5.52 (m, 1H), 6.90-7.01 (m, 5H), 7.10-7.15 (m, 2H), 7.25-7.35 (m, 2H), 7.42-7.52 (m, 3H)
MS $[M-Br]^+$: 458

Example 4
Preparation of (1*,3R)-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereoisomer 1)
Example 5
Preparation of (1*,3R)-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereoisomer 2)

2 g (0.00618 mol) of (3R)-1-methylpyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid (intermediate I-5) was dissolved in 40 ml of THF and 1.86 g (0.00927 mol) of (2-bromoethoxy)benzene was added. The mixture was refluxed for 81 hours and was

stirred for 64 hours at room temperature. During this procedure, an extra 2.46 g of (2-bromoethoxy)benzene (0.0122 mol) was added in several portions. After this time the reaction mixture was filtered and the solid obtained was washed with THF and ether. This solid (1.5 g) was treated with THF at the reflux temperature for 30 min, filtered without cooling and washed with THF and ether, giving 0.850 g (52.5%, based on a single isomer) of diastereoisomer 1.

The mother liquor from the first filtration was refluxed for a further 40 hours. The solid that formed was filtered (diastereoisomer 1) and the solution obtained was diluted with ether, giving an oily residue. The solvents were separated by decanting and the oily residue was dissolved in $CHCl_3$. This solution was evaporated giving 801 mg of a brownish-grey foam, which was purified by chromatography on silica gel using $CHCl_3$/isopropanol (50:50) as eluent. The appropriate fractions were combined and were evaporated, giving 0.47 g (29% based on a single isomer) of diastereoisomer 2.

Diastereoisomer 1. (First diastereoisomer obtained).
m.p.: 198.8-199.4°C.
^{1}H-NMR, diastereoisomer 1, 95:5.
^{1}H-NMR (DMSO-d_6): δ 2.10-2.25 (m, 1H), 2.65-2.82 (m, 1H), 3.20 (s, 3H), 3.60-3.90 (m, 5H), 3.95-4.05 (m, 1H), 4.38 (m, 2H), 5.56 (m, 1H), 6.95-7.05 (m, 5H), 7.10-7.20 (m, 2H), 7.30-7.42 (m, 2H), 7.45-7.60 (m, 3H).
MS $[M-Br]^+$: 444
(* Configuration not assigned)

Diastereoisomer 2. (Second diastereoisomer obtained)
m.p..: 85.9-87.6°C
^{1}H-NMR: diastereoisomer 2, 95:5
^{1}H-NMR (DMSO-d_6): δ 2.10-2.25 (m, 1H), 2.65-2.85 (m, 1H), 3.04 (s, 3H), 3.62-3.72 (m, 1H), 3.78-3.90 (m, 4H), 3.97-4.04 (m, 1H), 4.45 (m, 2H), 5.55 (m, 1H), 6.98-7.03 (m, 5H), 7.12-7.16 (m, 2H), 7.32-7.37 (m, 2H), 7.50-7.52 (m, 3H).
MS $[M-Br]^+$: 444
(* Configuration not assigned)

Example 11
Preparation of (1*,3R)-1-methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyl-oxy)pyrrolidinium bromide (diastereoisomer 1)

Example 12
Preparation of (1*,3R)-1-methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyl-oxy)pyrrolidinium bromide (diastereoisomer 2)

0.7 g (0.00226 mol) of (3R)-1-methylpyrrolidin-3-yl ester of 9H-xanthene-9-carboxylic acid (intermediate I-8) was dissolved in 15 ml of THF and 0.63 g (0.46 ml, 0.0034 mol) of (2-bromoethyl)benzene was added. The mixture was refluxed for 96 hours and was stirred for 72 hours at room temperature. During this procedure, an extra 1.26 g of (2-bromoethyl)benzene (0.92 ml, 0.0068 mol) was added in several portions. After this time, the reaction mixture was filtered and the solid obtained was washed with THF and ether. The yield was 0.301 g (53.7%, based on a single isomer) of diastereoisomer 1. The structure was confirmed by ^{1}H-NMR.

The mother liquor was evaporated and the oily residue (0.450 g) was purified by chromatography on silica gel, performing gradient elution with chloroform plus isopropanol as eluent (25 → 85%). The appropriate fractions were combined and were evaporated, giving 0.193 g (34.5% based on a single isomer) of diastereoisomer 2.

Diastereoisomer 1. (First diastereoisomer obtained)

m.p.: 232.3-233.1°C

HPLC: diastereoisomer 1, 92.5:7.5

^{1}H-NMR (DMSO-d_6): δ 2.0-2.15 (m, 1H), 2.55-2.70 (m, 1H), 3.0 (s, 3H), 3.0-3.10 (m, 2H), 3.45-3.75 (m, 5H), 3.85-3.92 (m, 1H), 5.30 (s, 1H), 5.36 (m, 1H), 7.10-7.50 (m, 13H).

MS $[M-Br]^+$: 414

(* Configuration not assigned).

Diastereoisomer 2. (Second diastereoisomer obtained)

m.p.: 79.6-81.2°C.

HPLC: diastereoisomer 2, 98.8:1.2

^{1}H-NMR (DMSO-d_6): δ 2.0-2.10 (m, 1H), 2.55-2.70 (m, 1H), 3.0-3.10 (m, 2H), 3.17 (s, 3H), 3.45-3.55 (m, 2H), 3.55-3.75 (m, 3H), 3.85-3.92 (m, 1H), 5.24 (s, 1H), 5.38 (m, 1H), 7.0-7.15 (m, 4H), 7.25-7.50 (m, 9H).

MS $[M-Br]^+$: 414

(* Configuration not assigned).

((*): Configuration not assigned; both the (1R) isomers and the (1S) isomers can form. Designated (1R) and (1S) for convenience).

Method (c)

The compounds of formula (V) which are methyl esters can be prepared by typical methods of esterification described in the bibliography starting from the corresponding

carboxylic acid, or following the methods described in documents WO 01/04118 A2 or ES P200003130, or according to the methods described in the bibliography: FR 2012964; Larsson. L et al. Acta Pharm. Suec. (1974), 11(3), 304-308; Nyberg, K. et al. Acta Chem. Scand. (1970), 24, 1590-1596; Cohen, V.I. et al. J. Pharm. Sciences (1992), 81, 326-329; E. Atkinson et al. J. Med. Chem. (1977), 20 (12), 1612-1617.

Intermediate I-1

Preparation of (3R)-1-(2-phenoxyethyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid

1.33 g of methyl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid (0.0052 mol) was dissolved in 40 ml of toluene. 1.08 g (0.0052 mol) of (3R)-1-(2-phenoxyethyl)pyrrolidin-3-ol (intermediate I-9) and 0.104 g (0.0026 mol) of NaH (60% dispersion in mineral oil) were added to this solution. The mixture was stirred for 30 min at room temperature, refluxed for 45 minutes and was then refluxed with continuous separation of the distillate for 1.5 hours replacing with fresh toluene when necessary. The cooled mixture was extracted with 2N HCl, the aqueous layer was alkalized with K_2CO_3 and was extracted with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4 and was evaporated, giving 1.77 g of an oil which was purified by chromatography on silica gel, eluting with chloroform/ethanol/NH_4OH (200:8:1). The appropriate fractions were combined and were evaporated, giving 1.22 g of the title product in the form of an oil (54.7%). This product solidified, forming the oxalate salt.

Oxalate salt of (3R)-1-(2-phenoxyethyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid: 1.03 g (0.0024 mol) of the free base was treated with oxalic acid (0.216 g, 0.0024 mol) in acetone/ether. A white solid was obtained, which was filtered and washed with ether. The yield was 0.91 g (73.4%).

m.p.: 134°C

^{1}H-NMR (DMSO-d_6): δ 1.80-1.95 (m, 1H), 2.20-2.35 (m, 1H), 2.90-3.25 (m, 5H), 3.25-3.35 (m, 1H), 4.16 (t, 2H), 5.33 (m, 1H), 6.95-7.0 (m, 5H), 7.10-7.15 (m, 2H), 7.25-7.35 (m, 2H), 7.45-7.50 (m, 2H).

MS $[M+1]^+$: 430

The methyl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid can be produced as described in Nyberg, K. et al. Acta Chem. Scand. (1970), 24, 1590-1596.

Intermediate I-2

Preparation of the (3R)-1-(3-phenoxypropyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithienylacetic acid

Prepared as described in intermediate I-1 starting from the methyl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid and (3R)-1-(3-phenoxypropyl)pyrrolidin-3-ol (intermediate I-10). The yield was 0.85 g (49%) of the title product in the form of an oil. A portion of this product solidified, forming the oxalate salt.

(3R)-1-(3-phenoxypropyl)pyrrolidin-3-yl oxalate of 2-hydroxy-2,2-dithien-2-ylacetic acid: 0.3 g (0.000676 mol) of the free base was treated with oxalic acid (0.060 g, 0.00067 mol) in acetone/ether. A solid was obtained, which was separated by filtration and washed with ether. The yield was 0.24 g (67%).

m.p.:115.6-117.2°C

^{1}H-NMR (DMSO-d_6): δ 1.90-2.05 (m, 3H), 2.20-2.40 (m, 1H), 2.90-3.25 (m, 5H), 3.40-3.50 (m, 1H), 4.0 (t, 2H), 5.38 (m, 1H), 6.90-7.0 (m, 5H), 7.10-7.15 (m, 2H), 7.25-7.35 (m, 2H), 7.45-7.50 (m, 2H).

MS $[M+1]^+$: 444

Intermediate I-3

Preparation of (3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid

Prepared as described in intermediate I-1 starting from the methyl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid and (3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-ol (intermediate I-11). The yield was 0.83 g (49.1%) of the title product in the form of an oil. A portion of this product solidified, forming the oxalate salt.

Oxalate salt of the (3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid: 0.3 g (0.00069 mol) of the free base was treated with oxalic acid (0.062 g, 0.00069 mol) in acetone/ether. A solid was obtained, which was filtered and washed with ether. The yield was 0.27 g (75%).

m.p.: 112.6-114.1°C

^{1}H-NMR (DMSO-d_6): δ 1.80-2.05 (m, 3H), 2.20-2.40 (m, 1H), 2.70-3.0 (m, 4H), 3.0-3.30 (m, 3H), 3.40-3.55 (m, 1H), 5.37 (m, 1H), 6.85-7.05 (m, 4H), 7.10-7.20 (m, 2H), 7.30-7.40 (m, 1H), 7.45-7.50 (m, 2H), 8-10 (broad band, 3H).

MS $[M+1]^+$: 434

Intermediate I-4

Preparation of (3R)-1-phenethylpyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-

ylacetic acid

Prepared as described in intermediate I-1 starting from the methyl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid and (3R)-1-phenethylpyrrolidin-3-ol (intermediate I-12). The yield was 0.98 g (50.5% of the title product).

m.p.: 114.3-115.7°C

^{1}H-NMR ($CDCl_3$): δ 1.85-1.95 (m, 1H), 2.20-2.35 (m, 1H), 2.50-2.62 (m, 1H), 2.62-2.82 (m, 6H), 2.85-3.0 (m, 1H), 4.92 (broad singlet, 1H, OH), 5.35 (m, 1H), 6.92-7.0 (m, 2H), 7.15-7.35 (m, 9H)

MS $[M+1]^+$: 414

Method (d)

Preparation of the methyl ester derivatives of formula (V) was described in method (c).

Intermediate I-5

Preparation of the (3R)-1-methylpyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid

1 g of the methyl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid (0.0039 mol) was dissolved in 30 ml of toluene. 0.394 g (0.0039 mol) of (3R)-1-methylpyrrolidin-3-ol (intermediate I-13) and 0.078 g (0.00195 mol) of NaH (60% dispersion in mineral oil) were added to this solution. The mixture was stirred for 30 minutes at room temperature, it was refluxed for one hour and then was refluxed with continuous separation of the distillate for 2 hours, adding fresh toluene when necessary. The cooled mixture was extracted with 2N HCl, the aqueous layer was washed with a small volume of ethyl acetate, it was alkalized with solid K_2CO_3 and was extracted 3 times with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and was evaporated. The yield was 0.73 g (58%) of the title product (structure confirmed by ^{1}H-NMR). This product was purified by chromatography on silica gel, eluting with chloroform/ethanol/NH_4OH (200:8:1). The appropriate fractions were combined and were evaporated, giving the title compound.

m.p.: 84°C.

^{1}H-NMR (DMSO-d_6): δ 1.62-1.75 (m, 1H), 2.10-2.32 (m, 2H), 2.21 (s, 3H), 2.45-2.55 (m, 1H), 2.55-2.70 (m, 2H), 5.18 (m, 1H), 6.95-7.0 (m, 2H), 7.05-7.15 (m, 2H), 7.32 (s, 1H, OH), 7.45-7.50 (m, 2H).

MS $[M+1]^+$: 324

Intermediate I-6

Preparation of the (3S)-1-methylpyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid

Prepared as described in intermediate I-5 starting from 0.98 g (0.00385 mol) of methyl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid in 30 ml of toluene, 0.39 g (0.00385 mol) of (3S)-1-methylpyrrolidin-3-ol (intermediate I-14) and 0.108 g (0.0027 mol) of NaH (60% dispersion in mineral oil). The yield was 0.31 g (25%) of the title product.

m.p.: 84°C

^{1}H-NMR (DMSO-d_6): δ (Equivalent to I-5)

MS $[M+1]^+$: 324

Intermediate I-7

Preparation of the 1-methylpyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid

Prepared as described in intermediate I-5 starting from methyl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid and 1-methylpyrrolidin-3-ol (commercially available). The yield was 0.96 g (30%).

^{1}H-NMR (DMSO-d_6): δ (Equivalent to I-5)

MS $[M+1]^+$: 324

Intermediate I-8

Preparation of the (3R)-1-methylpyrrolidin-3-yl ester of 9H-xanthene-9-carboxylic acid

2 g of 9H-xanthene-9-carboxylic acid (0.0088 mol) was dissolved in 30 ml of $CHCl_3$ (free ethanol). The solution was cooled to 0°C and 1.08 ml (0.0123 mol) of oxalyl chloride and one drop of DMF were added. The mixture was stirred and then left to warm to room temperature. After one hour at this temperature the solvents were evaporated and the residue was dissolved in $CHCl_3$ and was evaporated again. This procedure was repeated twice. The solid obtained (2.19 g) was dissolved in 20 ml of $CHCl_3$ and was added to a solution of 0.975 g (0.0097 mol) of (3R)-1-methylpyrrolidin-3-ol (intermediate I-13) in 15 ml of $CHCl_3$ cooled to 0-5°C. The reaction mixture was left to warm to room temperature and was stirred overnight. The solvent was evaporated and the residue was dissolved in toluene and then extracted with 2N HCl. The aqueous layer was alkalized with K_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and was evaporated to dryness, giving 2.53 g (93%) of the title product in the form of oil.

^{1}H-NMR ($CDCl_3$): δ 1.65-1.85 (m, 1H), 2.05-2.42 (m, 2H), 2.30 (s, 3H), 2.45-2.60 (m, 1H), 2.60-2.80 (m, 2H), 5.0 (s, 1H), 5.05-5.20 (m, 1H), 7.0-7.25 (m, 4H), 7.25-7.40 (m,

4H).
MS $[M+1]^+$: 310
This product was alkalized, forming the oxalate salt.

Oxalate salt of the (3R)-1-methylpyrrolidin-3-yl ester of 9H-xanthene-9-carboxylic acid: 2.53 g (0.0082 mol) of the free base was treated with oxalic acid (0.74 g, 0.0082 mol) in acetone/ether. A solid was obtained, which was filtered and washed with ether. The yield was 2.48 g (75.8%).
m.p.: 155.0-155.8°C.
MS $[M+1]^+$: 310

The sulphate salt of the 1-methylpyrrolidin-3-yl ester of 9H-xanthene-9-carboxylic acid was described by B.V. Franko et al., in J. Med. Pharm. Chem., (1960), 2 (5), 523-540.

Method (e)

Intermediate I-9
Preparation of (3R)-1-(2-phenoxyethyl)pyrrolidin-3-ol
0.5 g (0.0057 mol) of (3R)-pyrrolidin-3-ol (commercially available) was dissolved in 15 ml of acetonitrile. 1.32 g (0.0065 mol) of (2-bromoethoxy)benzene, 0.095 g (0.00057 mol) of KI and 1.57 g (0.114 mol) of K_2CO_3 were added to this solution. This mixture was stirred for 72 h at room temperature. The solid was filtered and the solvent was evaporated to dryness. $CHCl_3$ was added to the residue and the solution obtained was washed with water and brine, dried over Na_2SO_4 and the solvent was evaporated, obtaining 1.43 g of an oil. This product was purified by chromatography on silica gel, eluting with chloroform/methanol/NH_4OH (90:10:1). The yield was 1.08 g of the title compound (91.5%).
MS $[M+1]^+$: 208
^{1}H-NMR ($CDCl_3$): δ 1.80 (m, 1H), 2.20 (m, 1H), 2.40 (m, 1H), 2.65 (m, 1H), 2.75-3.10 (m, 4H), 4.10 (t, 2H), 4.35 (m, 1H), 6.95 (m, 3H), 7.30 (m, 2H).
(3R)-1-(2-phenoxyethyl)pyrrolidin-3-ol is described in document WO 9625417 A1.

Intermediate I-10
Preparation of (3R)-1-(3-phenoxypropyl)pyrrolidin-3-ol
Prepared as for intermediate I-9 starting from (3R)-pyrrolidin-3-ol (commercially available) and (3-bromopropoxy)benzene. The yield was 2.26 g (71.3%) of the title compound.

MS $[M+1]^+$: 222

^{1}H-NMR ($CDCl_3$): δ 1.75 (m, 1H), 2.0 (m, 2H), 2.10-2.40 (m, 2H), 2.50 (m, 1H), 2.60-2.80 (m, 3H), 2.90 (m, 1H), 4.0 (t, 2H), 4.35 (m, 1H), 6.90 (m, 3H), 7.30 (m, 2H).

Intermediate I-11

Preparation of (3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-ol

Prepared as for intermediate I-9 starting from (3R)-pyrrolidin-3-ol (commercially available) and 2-(3-bromopropyl)thiophene. The yield was 1.02 g (85%) of the title compound.

MS $[M+1]^+$: 212

^{1}H-NMR ($CDCl_3$): δ 1.65-2.0 (m, 3H), 2.10-2.35 (m, 2H), 2.40-2.60 (m, 3H), 2.70 (m, 1H), 2.80-3.0 (m, 3H), 4.35 (m, 1H), 6.80 (m, 1H), 6.90 (m.1H), 7.10 (m, 1H).

Intermediate I-12

Preparation of (3R)-1-phenethylpyrrolidin-3-ol

Prepared as for intermediate I-9 starting from (3R)-pyrrolidin-3-ol (commercially available) and (2-bromoethyl)benzene. The yield was 0.91 g (83.5%) of the title compound.

MS $[M+1]^+$: 192

1-phenethylpyrrolidin-3-ol is described in Zhu, Y-Q. et al., Yao Hsueh Hsueh Pao (1981), 16(3), 199-210.

^{1}H-NMR ($CDCl_3$): δ 1.65-1.85 (m, 1H), 2.10-2.40 (m, 2H), 2.55 (m, 1H), 2.65-2.90 (m, 5H), 2.90-3.05 (m, 1H), 4.35 (m, 1H), 7.10-7.40 (m, 5H).

Method (f)

Intermediate I-13

Preparation of (3R)-1-methyl-3-pyrrolidinol

15 g (0.172 mol) of (3R)-pyrrolidin-3-ol (commercially available) was dissolved in 240 ml of MeOH. This solution was cooled to 10-15°C and formaldehyde (124.5 ml of a 36% solution in water, diluted with 125 ml of MeOH) and $NaBH_4$ (16.27 g, 0.43 mol) were added in small portions, alternately for 1 h, maintaining the temperature at 10-15°C. After 20 min the mixture was heated to room temperature and the reaction continued for one hour. The reaction mixture was acidified with 2N HCl, it was stirred for 20 minutes and neutralized with solid $NaHCO_3$. The MeOH and most of the water evaporated, and the residue was diluted with a small amount of water, it was alkalized

with solid K_2CO_3 and it was extracted exhaustively with $CHCl_3$. The organic phases were combined and were dried over Na_2SO_4. The $CHCl_3$ was evaporated, giving an oil which was purified by Kugelrohr distillation at reduced pressure (0.2-0.3 mbar, 50-60°C in the stove), giving 14.91 g (85.6%) of the title product.

^{1}H-NMR ($CDCl_3$): δ 1.60-1.80 (m, 1H), 2.10-2.40 (m, 5H), 2.40-2.70 (m, 2H), 2.75-2.95 (m, 1H), 4.20-4.40 (m, 1H), 4.40-4.50 (bs, 1H, OH).

A 1 g sample of this material was treated with 1.5 g of (2R,3R)-tartaric acid in MeOH/ether, obtaining 2.3 g of the tartrate salt $[\alpha]_D = +10.6°$ (c=1, H_2O)[1].

[1] $[\alpha]^{22}{}_D = +11.1°$ (c=9.57, H_2O), Sleevi et al. J.Med. Chem., (1991), Vol 34, No. 4, 1314-1328).

Intermediate I-14

Preparation of (3S)-1-methyl-3-pyrrolidinol

Prepared as for intermediate I-13 starting from 2 g of (3S)-pyrrolidin-3-ol (commercially available). The yield was 1.65 g (71.1%) of a pale yellow oil, which did not necessarily have to be purified by distillation.

This material was treated with 2.5 g of (2S,3S)-tartaric acid in MeOH/ether, obtaining 3.65 g of the tartrate salt $[\alpha]_D = -11.3°$ (c=1, H_2O)[2].

[2] $[\alpha]^{22}{}_D = -11.5°$ (c=1, H_2O), Sleevi et al. J.Med. Chem., (1991), Vol 34, No. 4, 1314-1328).

Pharmaceutical compositions containing, as active principle, at least one pyrrolidinium derivative of formula (I) combined with a pharmaceutically acceptable vehicle or diluent are also included within the scope of the present invention. The composition is preferably given a suitable form for oral administration.

The pharmaceutically acceptable vehicles or diluents that are mixed with the active compound or compounds to form the composition of this invention are well known and the excipients used depend *inter alia* on the method of administration of the composition.

The compositions of this invention are preferably designed for oral administration. In this case, the composition for oral administration can be in the form of tablets, film-coated tablets, liquid for inhalation, powder for inhalation and aerosol for inhalation; containing, in all cases, one or more compounds of the invention; said preparations can

be produced by methods that are well known in the industry.

The diluents that can be used in the preparations of the composition include liquid and solid diluents that are compatible with the active principle, together with colouring or flavouring agents if desired. The tablets or film-coated tablets can conveniently contain between 1 and 500 mg, preferably from 5 to 300 mg of active principle. The compositions for inhalation can contain between 1 µg and 1000 µg, preferably from 10 µg to 800 µg of active principle. In human therapy, the dose of the compound of formula (I) depends on the desired effect and duration of the treatment; the doses for adults are generally between 3 mg and 300 mg per day in the case of tablets and 10 µg to 800 µg per day in the case of composition for inhalation.

Pharmacological action

The results of binding to human muscarinic receptors and the results of the bronchospasm test in guinea pigs were obtained as described below.

Investigations of human muscarinic receptors.

Binding of [3H]-NMS to human muscarinic receptors was carried out according to Waelbroeck et al. (1990), Mol. Pharmacol., 38: 267-273. The tests were carried out at 25°C. The preparations used were of membranes from stably transfected Chinese hamster ovary (CHO) K1 cells which express the genes of human M_3 muscarinic receptors.

For determination of IC_{50}, the membrane preparations were suspended in DPBS to a final concentration of 89 µg/ml for the M_3 subtype. The membrane suspension was incubated with the tritiated compound for 60 min. After incubation, the membrane fraction was separated by filtration and the bound radioactivity was determined. Nonspecific binding was determined by addition of atropine 10^{-4} M. At least six concentrations were analysed in duplicate to generate individual displacement curves.

The results obtained show that the compounds of the present invention have high affinity for the M_3 muscarinic receptors, preferably human muscarinic receptors. Thus, the IC_{50} of the preferred compounds of the invention is less than 35 nM. The more preferred compounds, such as the compounds of examples 1 to 8 described below, have an IC_{50} below 20 nM.

Test of bronchospasm in guinea pigs

The studies were carried out according to H. Konzett and F. Rössler (1940), Arch. Exp. Path. Pharmacol. 195: 71-74. Aqueous solutions of the agents to be tested were nebulized and were inhaled by ventilated and anaesthetized male guinea pigs (Dunkin-Hartley). The bronchial response to intravenous inoculation of acetylcholine was determined before and after administration of the drug and the changes in pulmonary resistance at different times were expressed as percentage inhibition of bronchospasm.

The compounds of the present invention inhibit the response of bronchospasm to acetylcholine with high potency and a prolonged time of action.

Specialists in this field will readily understand from the results described above that the compounds of the present invention have excellent M_3 antimuscarinic activity and can therefore be used in the treatment of diseases involving the M_3 muscarinic receptor, including respiratory disorders such as chronic obstructive pulmonary disease (COPD), bronchitis, bronchial hyperreactivity, asthma, cough and rhinitis; urologic disorders such as urinary incontinence, pollakiuria, neurologic or unstable bladder, cystospasm and chronic cystitis; gastrointestinal disorders such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulcers; and cardiovascular disorders, such as vagus-induced sinus bradycardia.

The present invention thus provides a compound of formula (I) or one of its pharmaceutically acceptable compositions, containing a compound of formula (I) for use in a method of treatment of a human being or an animal by therapy, in particular for the treatment of respiratory, urological or gastrointestinal diseases or disorders.

The present invention further provides the use of a compound of formula (I) or one of its pharmaceutically acceptable compositions containing a compound of formula (I) for the preparation of a medicinal product for the treatment of a respiratory, urological or gastrointestinal disease or disorder.

Moreover, the compounds of formula (I) and the pharmaceutical compositions that contain a compound of formula (I) can be used in a method for treating a respiratory, urological or gastrointestinal disease or disorder, said method comprising administering, to a human or animal patient requiring said treatment, an effective and non-toxic

amount of a compound of formula (I) or a composition containing a compound of formula (I).

Moreover, the compounds of formula (I) and the compositions that contain a compound of formula (I) can be used in combination with other drugs that are effective in the treatment of these diseases; for example with β_2 agonists, steroids, anti-allergic drugs, inhibitors of phosphodiesterase IV and/or inhibitors of leukotriene D4 (LTD4), for simultaneous, separate or sequential use in the treatment of a respiratory disease.

The present invention will be better illustrated with the following examples. The examples are only given for purposes of illustration and are not to be regarded as limiting the invention.

Example 1

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium trifluoroacetate

The title compound was obtained as a mixture of four stereoisomers according to methods (d) and (b) of intermediate I-7.
The yield in the final stage was 90 mg (30%).
MS $[M\text{-}CF3COO]^{+:}$ 428

Example 2

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide

The title compound was obtained as a mixture of two stereoisomers according to methods (c) and (a) of intermediate I-4. The yield in the final stage was 0.31 g (84.7%).
m.p.: 143.7-158.6°C
HPLC: mixture of diastereoisomers 44:56.
^{1}H-NMR (DMSO-d_6): δ 2.10-2.30 (m, 1H), 2.65-2.85 (m, 1H), 3.02-3.15 (m, 2H), 3.05 and 3.23 (s, 3H), 3.40-3.85 (m, 5H), 3.90-4.05 (m, 1H), 5.57 (m, 1H), 6.90-6.95 (m, 1H), 7.0-7.05 (m, 1H), 7.05-7.22 (m, 2H), 7.25-7.42 (m, 5H), 7.42-7.60 (m, 3H)
MS $[M\text{-}Br]^{+:}$ 428

Example 3

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)-pyrrolidinium bromide

The title compound was obtained as a mixture of two stereoisomers according to methods (c) and (a) of intermediate I-1. The yield in the final stage was 0.47 g (81.6%).
m.p.: 54.9-65.3°C.
^{1}H-NMR: mixture of diastereoisomers 50:50.
^{1}H-NMR (DMSO-d_6): δ 2.10-2.25 (m, 1H), 2.70-2.82 (m, 1H), 3.05 and 3.21 (s, 3H), 3.64-4.10 (m, 6H), 4.40 and 4.46 (m, 2H), 5.56 (m, 1H), 6.97-7.04 (m, 5H), 7.13-7.17 (m, 2H), 7.33-7.39 (m, 2H), 7.48-7.54 (m, 3H)
MS $[M-Br]^{+:}$ 444

Example 4 (described in method (b))
(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)-pyrrolidinium bromide (diastereoisomer 1)
The title compound was obtained as a single isomer according to methods (d) and (b) starting from intermediate I-5.
The yield in the final stage was 0.85 g (52.5% based on a single isomer).
m.p.: 198.8-199.4°C.
^{1}H-NMR: diastereoisomer 1, 95:5
^{1}H-NMR (DMSO-d_6): δ 2.10-2.25 (m, 1H), 2.65-2.82 (m, 1H), 3.20 (s, 3H), 3.60-3.90 (m, 5H), 3.95-4.05 (m, 1H), 4.38 (m, 2H), 5.56 (m, 1H), 6.95-7.05 (m, 5H), 7.10-7.20 (m, 2H), 7.30-7.42 (m, 2H), 7.45-7.60 (m, 3H).
MS $[M-Br]^{+:}$ 444
(* Configuration not assigned)

Example 5 (described in method (b))
(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)-pyrrolidinium bromide (diastereoisomer 2)
The title compound was obtained as a single isomer according to methods (d) and (b) starting from intermediate I-5.
The yield in the final stage was 0.47 g (29% based on a single isomer).
m.p.: 85.9-87.6°C
^{1}H-NMR: diastereoisomer 2, 95:5
^{1}H-NMR (DMSO-d_6): δ 2.10-2.25 (m, 1H), 2.65-2.85 (m, 1H), 3.04 (s, 3H), 3.62-3.72 (m, 1H), 3.78-3.90 (m, 4H), 3.97-4.04 (m, 1H), 4.45 (m, 2H), 5.55 (m, 1H), 6.98-7.03 (m, 5H), 7.12-7.16 (m, 2H), 7.32-7.37 (m, 2H), 7.50-7.52 (m, 3H).
MS $[M-Br]^{+:}$ 444
(* Configuration not assigned)

Example 6 (described in method (a))
(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-thien-2-ylpropyl)-pyrrolidinium bromide

The title compound was obtained as a mixture of two stereoisomers according to methods (c) and (a) starting from intermediate I-3. The yield in the final stage was 0.34 g (93.2%).

^{1}H-NMR: mixture of diastereoisomers 55:45

^{1}H-NMR (DMSO-d_6): δ 1.95-2.20 (m, 3H), 2.60-2.80 (m, 2H), 2.80-2.90 (m, 1H), 2.94 and 3.10 (s, 3H), 3.20- 3.45 (m, 2H), 3.45-3.95 (m, 4H), 5.52 (m, 1H), 6.90-7.05 (m, 4H), 7.10-7.20 (m, 2H), 7.37 (m, 1H), 7.40-7.55 (m, 3H).

MS $[M-Br]^{+:}$ 448

Example 7 (described in method (b))
3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)-pyrrolidinium bromide

The title compound was obtained as a mixture of four stereoisomers according to methods (d) and (b) starting from intermediate I-7. The yield in the final stage was 0.75 g (69.4%).

m.p.: 55.3-56.8°C.

^{1}H-NMR, mixture of diastereoisomers 56:44

^{1}H-NMR (DMSO-d_6): δ 2.05-2.30 (m, 3H), 2.60-2.80 (m, 1H), 2.96 and 3.12 (s, 3H), 3.40-3.50 (m, 1H), 3.50-3.82 (m, 4H), 3.85-4.0 (m, 2H), 4.0-4.10 (m, 1H), 5.52 (m, 1H), 6.90-7.01 (m, 5H), 7.10-7.15 (m, 2H), 7.25-7.35 (m, 2H), 7.42-7.52 (m, 3H)

MS $[M-Br]^{+:}$ 458

Example 8
(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)-pyrrolidinium bromide

The title compound was obtained as a mixture of two stereoisomers according to methods (c) and (a) starting from intermediate I-2. The yield in the final stage was 0.21 g (70%).

HPLC: mixture of diastereoisomers 59:41

^{1}H-NMR (DMSO-d_6): δ 2.05-2.30 (m, 3H), 2.65-2.80 (m, 1H), 3.0 and 3.15 (s, 3H), 3.40-3.50 (m, 1H), 3.50-3.85 (m, 4H), 3.85-4.0 (m, 2H), 4.0-4.10 (m, 1H), 5.55 (m, 1H), 6.90-7.05 (m, 5H), 7.10-7.20 (m, 2H), 7.25-7.35 (m, 2H), 7.45-7.55 (m, 3H).

MS $[M-Br]^+$: 458

Example 9 (described in method (a))
(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)-pyrrolidinium bromide (diastereoisomer 1)
The title compound was obtained as a single isomer according to methods (c) and (a) starting from intermediate I-2.
The yield in the final stage was 0.628 g (80.1% based on a single isomer).
m.p.: 86.2-89.6°C.
^{1}H-NMR: diastereoisomer 1 (diastereoisomer 2 not observed)
^{1}H-NMR (DMSO-d_6): δ 2.10-2.30 (m, 3H), 2.65-2.80 (m, 1H), 3.0 (s, 3H), 3.50-3.65 (m, 3H), 3.70-3.85 (m, 2H), 3.85-3.95 (m, 1H), 4.05 (m, 2H), 5.54 (m, 1H), 6.90-7.05 (m, 5H), 7.10-7.20 (m, 2H), 7.25-7.35 (m, 2H), 7.50-7.55 (m, 3H).
MS $[M-Br]^+$: 458
(* Configuration not assigned)

Example 10 (described in method (a))
(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)-pyrrolidinium bromide (diastereoisomer 2)
The title compound was obtained as a single isomer according to methods (c) and (a) starting from intermediate I-2.
The yield in the final stage was 0.559 g (71.3% based on a single isomer).
m.p.: 87.1-89.0°C.
^{1}H-NMR: diastereoisomer 2 (diastereoisomer 1 not observed)
^{1}H-NMR (DMSO-d_6): δ 2.05-2.30 (m, 3H), 2.65-2.80 (m, 1H), 3.15 (s, 3H), 3.40-3.55 (m, 2H), 3.55-3.80 (m, 3H), 3.95 (m, 3H), 5.55 (m, 1H), 6.90-7.05 (m, 5H), 7.05-7.20 (m, 2H), 7.30-7.40 (m, 2H), 7.45-7.50 (m, 3H).
MS $[M-Br]^+$: 458
(* Configuration not assigned)

Example 11 (described in method (b))
(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereoisomer 1)
The title compound was obtained as a single isomer according to methods (d) and (b) starting from intermediate I-8.
The yield in the final stage was 0.301 g (53.7% based on a single isomer).
m.p.: 232.3-233.1°C
HPLC: diastereoisomer 1, 92.5:7.5
^{1}H-NMR (DMSO-d_6): δ 2.0-2.15 (m, 1H), 2.55-2.70 (m, 1H), 3.0 (s, 3H), 3.0-3.10 (m,

2H), 3.45-3.75 (m, 5H), 3.85-3.92 (m, 1H), 5.30 (s, 1H), 5.36 (m, 1H), 7.10-7.50 (m, 13H).
MS $[M-Br]^+$: 414
(* Configuration not assigned)

Example 12 (described in method (b))
(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereoisomer 2)
The title compound was obtained as a single isomer according to methods (d) and (b) starting from intermediate I-8.
The yield in the final stage was 0.193 g (34.5% based on a single isomer).
m.p.: 79.6-81.2°C.
HPLC: diastereoisomer 2, 98.8:1.2
^{1}H-NMR (DMSO-d_6): δ 2.0-2.10 (m, 1H), 2.55-2.70 (m, 1H), 3.0-3.10 (m, 2H), 3.17 (s, 3H), 3.45-3.55 (m, 2H), 3.55-3.75 (m, 3H), 3.85-3.92 (m, 1H), 5.24 (s, 1H), 5.38 (m, 1H), 7.0-7.15 (m, 4H), 7.25-7.50 (m, 9H).
MS $[M-Br]^+$: 414
(* Configuration not assigned)

((*): Configuration not assigned; both the (1R) isomers and the (1S) isomers of the aforementioned compounds may form. Designated (1R) and (1S) for convenience).

The following examples illustrate pharmaceutical compositions according to the present invention and methods for their preparation.

Example 13
Preparation of a pharmaceutical composition: tablets
Formulation:

Compound of the present invention	5.0 mg
Lactose	113.6 mg
Microcrystalline cellulose	28.4 mg
Light silica	1.5 mg
Magnesium stearate	1.5 mg

Using a mixing machine, 15 g of the compound of the present invention was mixed with 340.8 g of lactose and 85.2 g of microcrystalline cellulose. The mixture was moulded by compression using a roller compactor to obtain a compressed material in the form of

flakes. The compressed material in the form of flakes was pulverized using a hammer mill, and the pulverized material was sieved through a sieve of mesh 20. A portion of 4.5 g of light silica and 4.5 g of magnesium stearate was added to the sieved material and mixed. The mixed product was processed in a tableting machine equipped with a die/punch system of 7.5 mm diameter, obtaining 3000 tablets each weighing 150 mg.

Example 14

Preparation of a pharmaceutical composition: coated tablets

Formulation:

Compound of the present invention	5.0 mg
Lactose	95.2 mg
Maize starch	40.8 mg
Polyvinylpyrrolidone K25	7.5 mg
Magnesium stearate	1.5 mg
Hydroxypropylcellulose	2.3 mg
Polyethylene glycol 6000	0.4 mg
Titanium dioxide	1.1 mg
Purified talc	0.7 mg

Using a fluidized-bed granulator, 15 g of the compound of the present invention was mixed with 285.6 g of lactose and 122.4 g of maize starch. Separately, 22.5 g of Polyvinylpyrrolidone was dissolved in 127.5 g of water to prepare a fixing solution. Using a fluidized-bed granulator, the fixing solution was sprayed on the aforementioned mixture, obtaining granules. A portion of 4.5 g of magnesium stearate was added to the granules obtained and mixed. The mixture obtained was processed in a tableting machine equipped with a biconcave die/punch system of 6.5 mm diameter, obtaining 3000 tablets each weighing 150 mg.

Separately, a coating solution was prepared by suspending 6.9 g of hydroxypropylmethylcellulose 2910, 1.2 g of polyethylene glycol 6000, 3.3 g of titanium dioxide and 2.1 g of purified talc in 72.6 g of water. Using a high-coating system, the 3000 tablets previously prepared were coated with the coating solution, giving the film-coated tablets, each weighing 154.5 mg.

Example 15

Preparation of a pharmaceutical composition: liquid for inhalation

Formulation:

Compound of the present invention	400 µg

Physiological saline solution	1 ml

A portion of 40 mg of the compound of the present invention was dissolved in 90 ml of physiological saline solution and the resulting solution was made up to a total volume of 100 ml with the same saline solution, it was distributed in 1-ml portions in vials with a capacity of 1 ml and was then sterilized at 115°C for 30 minutes, giving a liquid for inhalation.

Example 16

Preparation of a pharmaceutical composition: powder for inhalation

Formulation:

Compound of the present invention	200 µg
Lactose	4000 µg

A portion of 20 g of the compound of the present invention was mixed uniformly with 400 g of lactose and a 200 mg portion of this mixture was packaged in a powder inhaler for use exclusively for production of a powder for inhalation.

Example 17

Preparation of a pharmaceutical composition: aerosol for inhalation

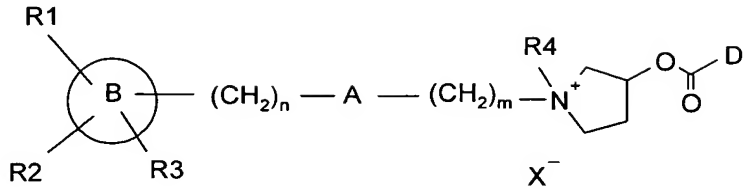
Formulation:

Compound of the present invention	200 µg
Dehydrated ethanol (absolute) USP	8400 µg
1,1,1,2-Tetrafluoroethane (HFC-134A)	46 810 µg

The concentrate of active principle was prepared by dissolving 0.0480 g of the compound of the present invention in 2.0160 g of ethanol. The concentrate was added to a suitable filling apparatus. The concentrate of active principle was distributed in an aerosol container, the space at the top of the container was purged with nitrogen or HFC-134A vapour (the purge ingredients must not contain more than 1 ppm of oxygen) and was sealed hermetically with a valve. Then 11.2344 g of the HFC-134A propellant was introduced under pressure into the hermetically sealed container.

CLAIMS

1.- Compound of formula (I):



(I)

in which

B is a phenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl or biphenyl group or a 5- to 10-membered heteroaromatic group that contains one or more heteroatoms selected from N, O or S;

R^1, R^2 and R^3 each represent, independently, a hydrogen or a halogen atom, or a hydroxy, phenyl, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-NHCOR^5$, $-CONR^5R^6$, -CN, $-NO_2$, $-COOR^5$ or $-CF_3$ group or a linear or branched lower alkyl group, optionally substituted;

or R^1 and R^2 together form an aromatic or alicyclic ring or a heterocyclic group;

R^5 and R^6 each represent, independently, a hydrogen atom, a linear or branched lower alkyl group, optionally substituted, or together form an alicyclic ring;

n is an integer from 0 to 4;

A represents a group selected from $-CH_2-$, $-CH=CR^7-$, $-CR^7=CH-$, $-CR^7R^8-$, -CO-, -O-, -S-, -S(O)-, $-S(O)_2-$ and $-NR^7-$, in which R^7 and R^8 each represent, independently, a hydrogen atom, a linear or branched lower alkyl group, optionally substituted, or together form an alicyclic ring;

m is an integer from 0 to 8;

R^4 represents a lower alkyl group;
D represents a group of formula i) or ii)

i) ii)

in which

R^9 represents a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl or 3-thienyl;

R^{10} represents a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl or C_3-C_7 cycloalkyl;

and R^{11} represents a hydrogen atom or a hydroxy, methyl or $-CH_2OH$ group;

the cyclic groups represented by R^9 and R^{10} being optionally substituted with one or two substituents selected from halogen, linear or branched lower alkyl optionally substituted, hydroxy, alkoxy optionally substituted, nitro, cyano, $-CO_2R^{12}$ or $-NR^{12}R^{13}$, in which R^{12} and R^{13} are identical or different and are selected from hydrogen and linear or branched lower alkyl groups, optionally substituted;

Q represents a single bond or a $-CH_2-$, $-CH_2-CH_2-$, $-O-$, $-O-CH_2-$, $-S-$, $-S-CH_2-$ or $-CH=CH-$ group;

X^- represents a pharmaceutically acceptable anion of a monovalent or polyvalent acid;

including all the individual stereoisomers and mixtures thereof;

with the condition that in the compounds in which B is phenyl, R^9 is unsubstituted phenyl, R^{10} is unsubstituted phenyl or unsubstituted C_3-C_7 cycloalkyl, R^{11} is hydrogen or hydroxy, and then the sequence $-(CH_2)_n-A-(CH_2)_m-$ cannot be one of methylene, ethylene or propylene.

2.- Compound according to Claim 1, characterized in that B represents a phenyl, pyrrolyl, thienyl, furyl, biphenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, imidazolyl or benzothiazolyl group.

3.- Compound according to Claim 2, characterized in that B represents a phenyl, thienyl or pyrrolyl group.

4.- Compound according to any one of the preceding claims, characterized in that R^1, R^2 and R^3 each represent, independently, a hydrogen atom or a halogen atom, or a hydroxy, methyl, tert-butyl, $-CH_2OH$, 3-hydroxypropyl -OMe, $-NMe_2$, -NHCOMe, $-CONH_2$, -CN, $-NO_2$, -COOMe or $-CF_3$ group.

5.- Compound according to Claim 4, characterized in that R^1, R^2 and R^3 each represent, independently, hydrogen, fluorine, chlorine or hydroxy.

6.- Compound according to any one of the preceding claims, characterized in that n = 0 or 1; m is an integer from 1 to 6; and A represents a $-CH_2-$, -CH=CH-, -CO-, -NMe-, -O- or -S- group.

7.- Compound according to Claim 6, characterized in that A is a $-CH_2-$, -CH=CH- or -O- group.

8.- Compound according to Claim 6, characterized in that the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylalyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 3-thien-2-ylpropyl, 4-oxo-4-thien-2-ylbutyl, 2-benzyloxyethyl, 3-o-tolyloxypropyl, 3-(3-cyanophenoxy)propyl, 3-(methylphenylamino)propyl, 3-phenylsulphanylpropyl, 4-oxo-4-phenylbutyl, 4-(4-fluorophenyl)-4-oxobutyl, 3-(2-chlorophenoxy)propyl, 3-(2,4-difluorophenoxy)propyl, 3-(4-methoxyphenoxy)propyl and 3-(benzo[1,3]dioxol-5-yloxy)propyl.

9.- Compound according to Claim 8, characterized in that the pyrrolidinium group is substituted on the nitrogen atom with a C_1-C_4 alkyl group and another group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylalyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 4-(4-fluorophenyl)-4-oxobutyl or 3-thien-2-ylpropyl.

10.- Compound according to any one of the preceding claims, characterized in that D is a group of formula i), and in that R^9 is a group selected from phenyl, 2-thienyl or 2-furyl; R^{10} is a group selected from phenyl, 2-thienyl, cyclohexyl

or cyclopentyl; and R^{11} is a hydroxy group.

11.- Compound according to any one of the Claims 1 to 9, characterized in that D is a group of formula ii), and in that Q is a single bond or an oxygen atom and R^{11} is a hydrogen atom or a hydroxy group.

12.- Compound according to any one of the preceding claims, characterized in that X^- is chloride, bromide, trifluoroacetate or methanesulphonate.

13.- Compound according to any one of the preceding claims, characterized in that the carbon in the 3 position of the pyrrolidinium ring has the R configuration.

14.- Compound according any one of the Claims 1 to 12, characterized in that the carbon in the 3 position of the pyrrolidinium ring has the S configuration.

15.- Compound according to any one of the Claims 1 to 10 and 12 to 14, characterized in that D is a group of formula i) and the carbon substituted with R^9, R^{10} and R^{11} has the R configuration.

16.- Compound according to any one of the Claims 1 to 10 and 12 to 14, characterized in that D is a group of formula i) and the carbon substituted with R^9, R^{10} and R^{11} has the S configuration.

17.- Compound according to any one of the preceding claims, which is a single isomer.

18.- Compound according to Claim 1, which is one of:

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium trifluoroacetate

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-thien-2-ylpropyl)pyrrolidinium bromide

3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl) pyrrolidinium

bromide
3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenylalil)pyrrolidinium trifluoroacetate
3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(4-oxo-4-thien-2-ylbutil)pyrrolidinium trifluoroacetate
1-[4-(4-Fluorophenyl)-4-oxobutil]-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-methylpyrrolidinium trifluoroacetate
1-Ethyl-3-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-hydroxyphenoxy)propyl]pyrrolidinium trifluoroacetate
3-(2-Hydroxy-2,2-dithien-2-yl-acetoxy)-1-methyl-1-(3-pyrrol-1-ylpropyl)pyrrolidinium trifluoroacetate
3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-[6-(4-phenylbutoxy)hexyl]pyrrolidinium trifluoroacetate
1-(2-Benzyloxyethyl)-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium trifluoroacetate
1-[3-(3-Cyanophenoxy)propyl]-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium trifluoroacetate
3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methyl-1-[3-(naphthalen-1-yloxy)propyl]pyrrolidinium trifluoroacetate
3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methyl-1-[3-(methylphenylamino)propyl]pyrrolidinium trifluoroacetate
3-(2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-ethyl-1-(3-phenylsulphanylpropyl)pyrrolidinium trifluoroacetate
1-[3-(Benzothiazol-2-yloxy)propyl]-3-(2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy)-1-methylpyrrolidinium trifluoroacetate
3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide
3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(2,4,6-trimethylphenoxy)propyl]pyrrolidinium trifluoroacetate
1-[3-(2-Chlorophenoxy)propyl]-3-(2-cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methylpyrrolidinium trifluoroacetate
3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(3-trifluoromethylphenoxy)propyl]pyrrolidinium trifluoroacetate
1-[3-(Biphenyl-4-yloxy)propyl]-3-(2-cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methylpyrrolidinium trifluoroacetate
3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-[3-(2,4-difluorophenoxy)propyl]-1-methylpyrrolidinium trifluoroacetate

3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-ethyl-1-[3-(4-methoxyphenoxy)propyl]-pyrrolidinium trifluoroacetate
3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyl]pyrrolidinium trifluoroacetate
3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1-methyl-1-[3-(1-methyl-1H-imidazol-2-ylsulphanyl)propyl]pyrrolidinium trifluoroacetate
1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide
1-Methyl-1-(3-phenoxypropyl)-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide
1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate
1-[3-(2-Carbamoylphenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate
1-[3-(3-Dimethylaminophenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate
1-[3-(4-Acetylaminophenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate
1-[3-(4-Methoxycarbonylphenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate
1-Methyl-1-[3-(4-nitrophenoxy)propyl]-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium trifluoroacetate, and
1-[3-(4-Hydroxymethylphenoxy)propyl]-1-methyl-3-(9H-xanthen-9-ylcarboniloxy)pyrrolidinium trifluoroacetate.

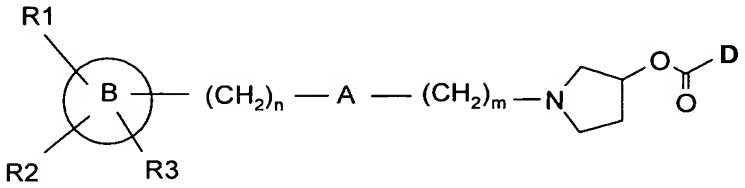
19.- Compound according to Claim 1, which is one of:

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide
(1*, 3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide (diastereoisomer 1)
(1*, 3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide (diastereoisomer 2)
(3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-phenethylpyrrolidinium bromide
(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)-pyrrolidinium bromide
(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereoisomer 1)

(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereoisomer 2)
(3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide
(1*,3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereoisomer 1)
(1*,3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(2-phenoxyethyl)pyrrolidinium bromide (diastereoisomer 2)
(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-thien-2-ylpropyl)pyrrolidinium bromide
(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide
(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 1)
(1*,3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 2)
(3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide
(3R)-3-[(2R)-2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy]-1-ethyl-1-(3-phenylsulphanylpropyl)pyrrolidinium trifluoroacetate
(3S)-3-[(2R)-2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy]-1-ethyl-1-(3-phenylsulphanylpropyl)pyrrolidinium trifluoroacetate
(3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide
(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 1)
(1*,3R)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 2)
(3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide
(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 1)
(1*,3S)-3-[(2R)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide (diastereoisomer 2)
(3R)-3-[(2S)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-phenoxypropyl)pyrrolidinium bromide
(3S)-3-[(2S)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1-methyl-1-(3-

phenoxypropyl)pyrrolidinium bromide
(3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide
(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereoisomer 1)
(1*,3R)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide (diastereoisomer 2), and
(3S)-1-Methyl-1-phenethyl-3-(9H-xanthen-9-ylcarbonyloxy)pyrrolidinium bromide.

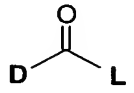
20.- Method of producing a compound of formula (I), as defined in any one of the preceding claims, which comprises reacting an alkylating agent of formula R4-W with an intermediate of formula (II)



(II)

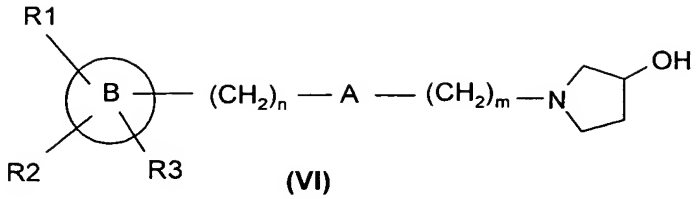
in which m, n, A, B, D, R1, R2, R3 and R4 are as defined in Claim 1 and W is any suitable removable group.

21.- Method according to Claim 20, characterized in that the compound of formula (II) is obtained by reaction of a compound of formula (V)



(V)

in which D is as defined in Claim 1 and L is a removable group, with a compound of formula (VI)



(VI)

in which m, n, A, B, D, R1, R2 and R3 are as defined in Claim 1.

22.- Compound of formula (II) which is one of:

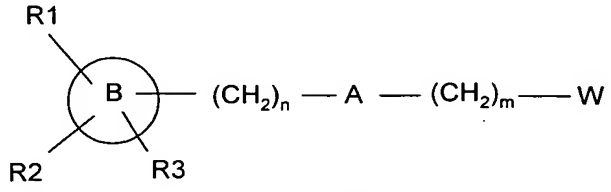
(3R)-1-(2-phenoxyethyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid
(3R)-1-(3-phenoxypropyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid
(3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid, and
(3R)-1- phenethylpyrrolidin-3-yl ester of 2-hydroxy-2,2-dithien-2-ylacetic acid.

23.- Compound of formula (VI) which is one of

(3R)-1-(3-phenoxypropyl)pyrrolidin-3-ol and
(3R)-1-(3-thien-2-ylpropyl)pyrrolidin-3-ol.

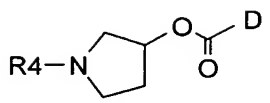
24.- Method of producing a compound of formula (I), as defined in any one of the preceding claims, comprising

reacting an alkylating agent of formula (IV):



(IV)

in which m, n, A, B, D, R1, R2 and R3 are as defined in Claim 1 and W represents any suitable removable group, with an intermediate of formula (III)



(III)

in which R4 and D are as defined in Claim 1.

25.- Pharmaceutical composition that contains a compound according to any one of the Claims 1 to 19, mixed with a pharmaceutically acceptable excipient or vehicle.

26.- Compound according to any one of the Claims 1 to 19, for the treatment of a pathological state or disease that is amenable to treatment by antagonism of the M_3 muscarinic receptors.

27.- Use of a compound according to any one of the Claims 1 to 19 in the preparation of a medicinal product for the treatment of a pathological state or disease that is amenable to treatment by antagonism of the M_3 muscarinic receptors.

28.- Use according to Claim 27, characterized in that the pathological state is a respiratory, urological or gastrointestinal disease or disorder.

29.- Method of treating a subject affected by a pathological state or disease that is amenable to treatment by antagonism of the M_3 muscarinic receptors, which comprises administering an effective amount of a compound as defined in any one of the Claims 1 to 19 to said subject.

30.- Method according to Claim 29, characterized in that the pathological state is a respiratory, urological or gastrointestinal disease or disorder.

31.- Combination of products, comprising:
(i) a compound according to any one of the Claims 1 to 19; and
(ii) another compound that is effective in the treatment of a respiratory, urological or gastrointestinal disease or disorder, for simultaneous, separate or sequential use.

32.- Combination of products according to Claim 29, comprising:
(i) a compound according to any one of the Claims 1 to 19; and
(ii) a β_2 agonist, steroid, anti-allergic drug, inhibitor of phosphodiesterase IV and/or

antagonist of leukotriene D4 (LTD4) for simultaneous, separate or sequential use in the treatment of a respiratory disease.

Certification

I, Sonia Fernández Boto
Sworn Translator for the English language, hereby certify that the foregoing is a true and complete translation into English of a document drawn up in Spanish.
In Madrid on this 3 day of July 2006

SIGNATURE

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